Intermediates for the the synthesis of Ethyl 3-{[(2-{[(4-{N'-hexyloxycarbonyl carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl] (pyridin-2-yl-amino)propanoate mesylate

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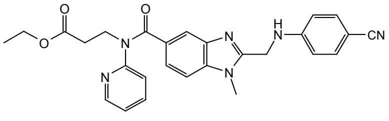
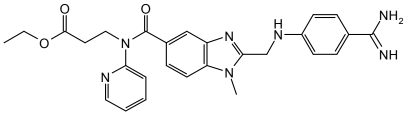
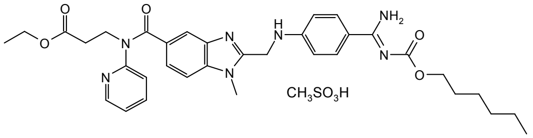
Intermediates for the the synthesis of Ethyl 3-{[(2-{[(4-{N'-hexyloxycarbonyl carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl] (pyridin-2-yl-amino)propanoate mesylate

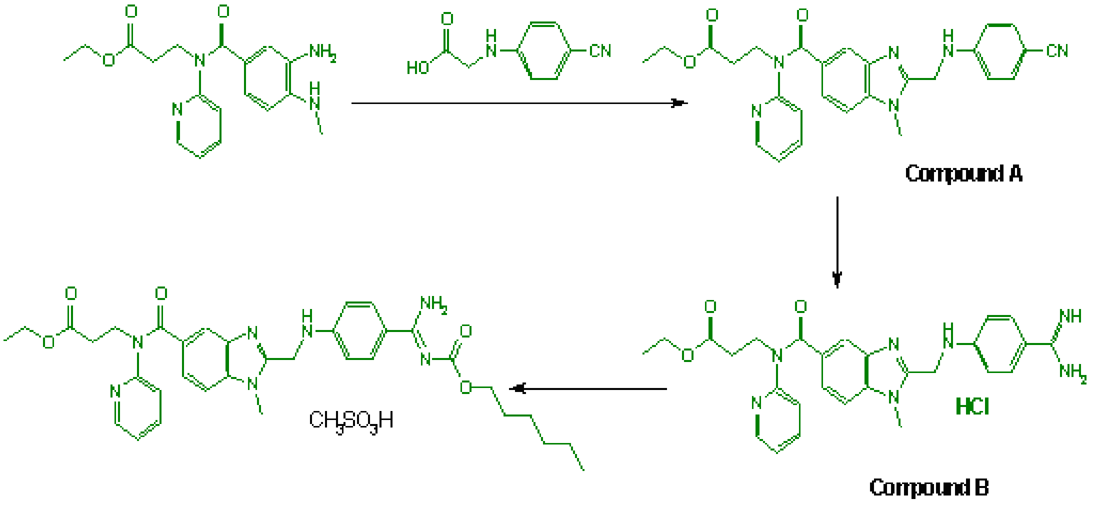
β-Alanine, N-[[2-[[(4-cyanophenyl)amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-, ethyl ester (referred , herein as Compound A), and β-Alanine, N-[[2-[[[4-(aminoiminomethyl)-phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-, ethyl ester (referred herein as Compound B) are intermediates for the synthesis of ethyl Ethyl 3-{[(2-{[(4-{N'-hexyloxycarbonyl carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl] (pyridin-2-yl-amino)propanoate mesylate (referred herein as Compound 1).


Compound A


Compound B


Compound 1

Following reaction scheme has been followed for the preparation of compound 1



Reported herein processes for the preparation of Compound A and its purification via various salts, as well as crystalline form of Compound B. The different salts of Compound –A , as such or after making free base have been used for the preparation of different forms of Compound B described herein which have also been used for the synthesis of **Ethyl 3-{[(2-{[(4-{N'-hexyloxycarbonyl carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl] (pyridin-2-yl-amino)propanoate mesylate**

Process for preparing Compound A

Step 1: Crude Compound A

Compound A is prepared by the reaction of N-(4-Cyanophenyl)glycine with Carbonyldiimidazole (CDI) in an organic solvents, such as dichloromethane at room temperature in presence of nitrogen to result an activated ester of N-(4-cyanophenyl)glycine which was further reacted with β-Alanine, N-[3-amino-4-(methylamino)benzoyl]-N-2-pyridinyl-, ethyl ester at 0 to 35 C , followed by cyclisation in acetic acid on heating at 30- 100 C to give compound A. From the reaction mass, compound A crude has been isolated by usual work up.

Step 2: Purification of crude Compound A by a acid salt preparation

Preparation of Compound A succinate, fumarate, tosylate, maleate & malonate salts:

A solution of Compound A (0.01 to 0.1 mole) in a solvent (5-10 vol) was heated to 45-55ºC and an acid (0.01 to 0.1 mole) in 1-2 vol. of solvent was added drop wise. The mixture was stirred for 0.5-1 hour at 45-55°C, then the reaction mass was cooled to RT and was stirred for 1-2 hours.

The reaction mass was filtered and the product was washed with 1-2 vol. of solvent. Dried under vacuum to give the corresponding salt in 60- 80%, having ; HPLC Purity >: 95%

Wherein, Solvent is selected from methanol, ethanol, isopropyl alcohol, ethyl acetate, n-butyl acetate, Acetonitrile, and mixture thereof.

Acid is selected from Succinic acid, Fumaric acid, p-toluenesulfonic acid, Maleic acid and Malonic acid.

X-Ray powder diffraction pattern of obtained acid salts of compound A are given below:

X-Ray powder diffraction pattern of Compound A Succinate salt comprising main peaks at: 7.5, 8.5, 11.3, 15.1, 16.0, 17.3, 18.7, 21.4, 24.3, 25.3 and 25.9 ± 0.2 degrees 2θ.

The X-Ray powder diffraction pattern is shown in Figure 1.

X-Ray powder diffraction pattern of Compound A fumarate salt comprising main peaks at: 8.5, 11.3, 11.8, 16.1, 16.7, 17.3, 21.7, 25.4 and 28.7 ± 0.2 degrees 2θ .

The X-Ray powder diffraction pattern is shown in Figure 2.

X-Ray powder diffraction pattern of Compound A tosylate salt comprising main peaks at: 4.9, 9.8, 13.4, 16.9, 18.3, 20.1, 20.8, 21.5, 22.5 and 25.0 ± 0.2 degrees 2θ

The X-Ray powder diffraction pattern is shown in Figure 3.

X-Ray powder diffraction pattern of Compound A maleat salt comprising main peaks at: 7.0, 9.4, 16.2, 17.9, 21.9, 24.5, 25.1 and 26.6 ± 0.2 degrees 2θ.

The X-Ray powder diffraction pattern is shown in Figure 4.

X-Ray powder diffraction pattern of Compound A malonate salt comprising main peaks at: 7.1, 15.9, 17.8, 20.2, 21.4, 24.4, 25.0 and 25.6 ± 0.2 degrees 2θ.

The X-Ray powder diffraction pattern is shown in Figure 5.

Crystalline form of Compound B

Example -1: Preparation of Compound B HCl salt

To a suspension of Compound A in ethanol, the HCl gas is added at 0- 45 C, the reaction was stirred to complete the reaction

after completion of reaction ethanolic ammonia was added and stir to completion of reaction . Compound B HCL crude was isolated from the reaction mixture after addition of IPA by filtration and distillation of solvent. The crude Compound B.HCl was re crystallized from the mixture of ethanol and IPA to give a crystalline compound B HCl as a IPA solvate , having IPA contents 25000 to 60000 PPM the ethanol contents less than 15000ppm.

Resulting crystals of Compound B HCl salt IPA solvate or as described in are crystalline form I (published in IPCOM000214414D). The X-Ray powder diffraction pattern is shown in Figure 6.

Example -2: Preparation of Compound B.HCl.2H_2O :

Compound B.hydrochloride IPA solvate, as described above, on stirring in water at 0-40 C, after filtering and drying resulted in the Compound B.HCl.2H2O in 80-85% yield.

This can also be prepared by stirring the compound B .HCl IPA solvate as described above in the mixture of water miscible organic solvents such as acetone.

Resulting crystals of Compound B.HCl.$\underline{2H_2O}$ salt are crystalline form II (published in IPCOM000214414D). The X-Ray powder diffraction pattern is shown in Figure 7.

Example-3: Preparation of Anhydrous Compound B.HCl

Compound B.HCl.IPA-EtOH solvate (obtained by Example-1) is stirred in acetone at 0-40 C for 2-8 hrs and filteedr and dried to give anhydrous Compound B.HCl, having LOD less than 2%, in 80- 90% yield.

X-ray powder diffraction method:

The X-ray powder diffraction patterns were performed on *BRUKER* D8 *Advance* X-Ray powder diffractometer with Cu-tube and LynxEye position sensitive detector, using PMMA specimen holder ring.

The scanning parameters were as follows:

Sample:	Spin mode, rotation speed: 60 rpm.
Range:	2-40 degrees two-theta
Scan mode:	Continuous scan
Step size:	0.05±0.005 deg.
Time/Step:	0.1 sec.
Divergence slit:	1

Figure 1: X-Ray powder diffraction pattern of Compound A succinate salt

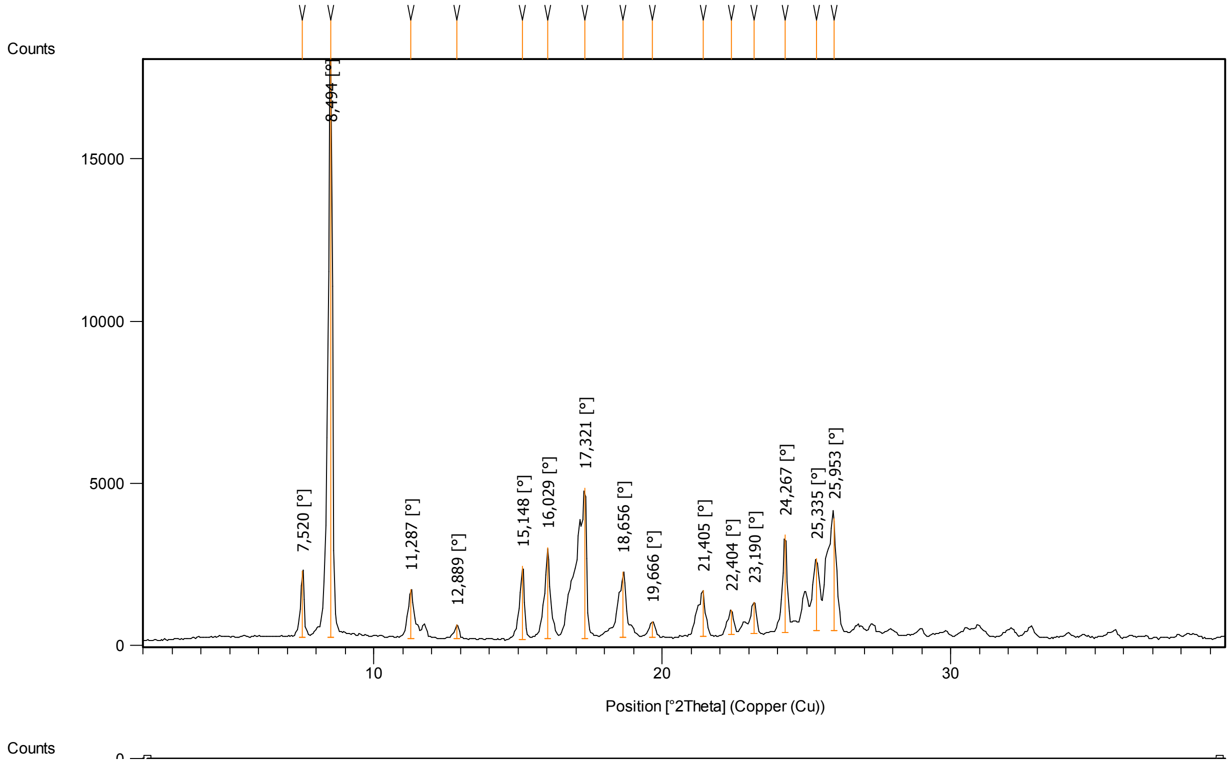


Figure 2: X-Ray powder diffraction pattern of Compound A fumarate salt

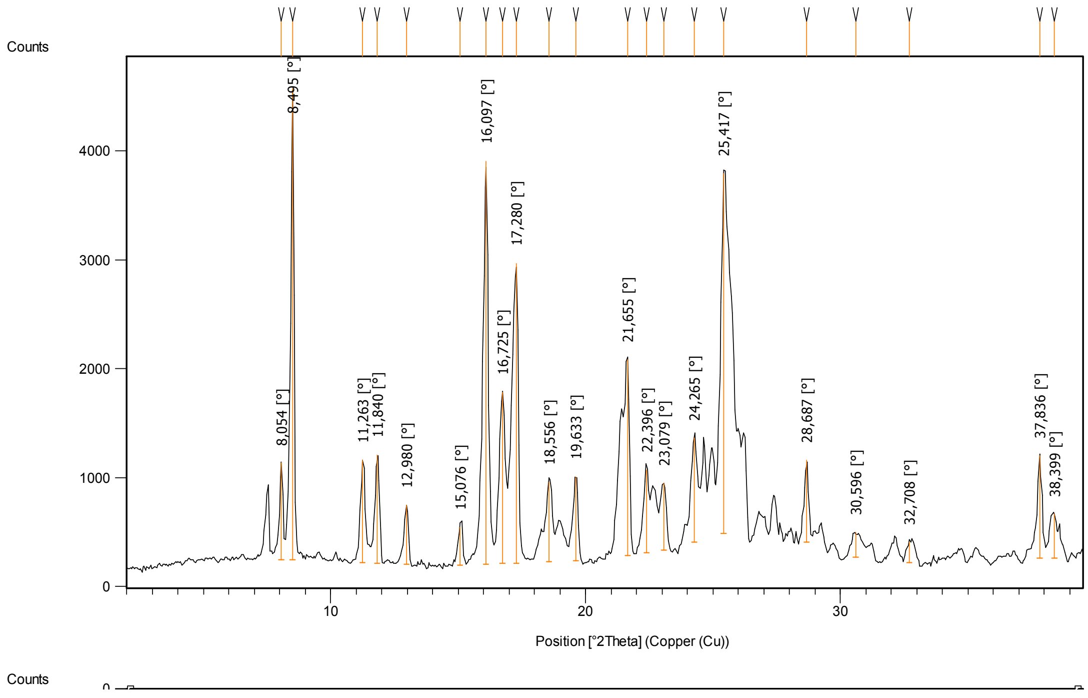


Figure 3: X-Ray powder diffraction pattern of Compound A tosylate salt

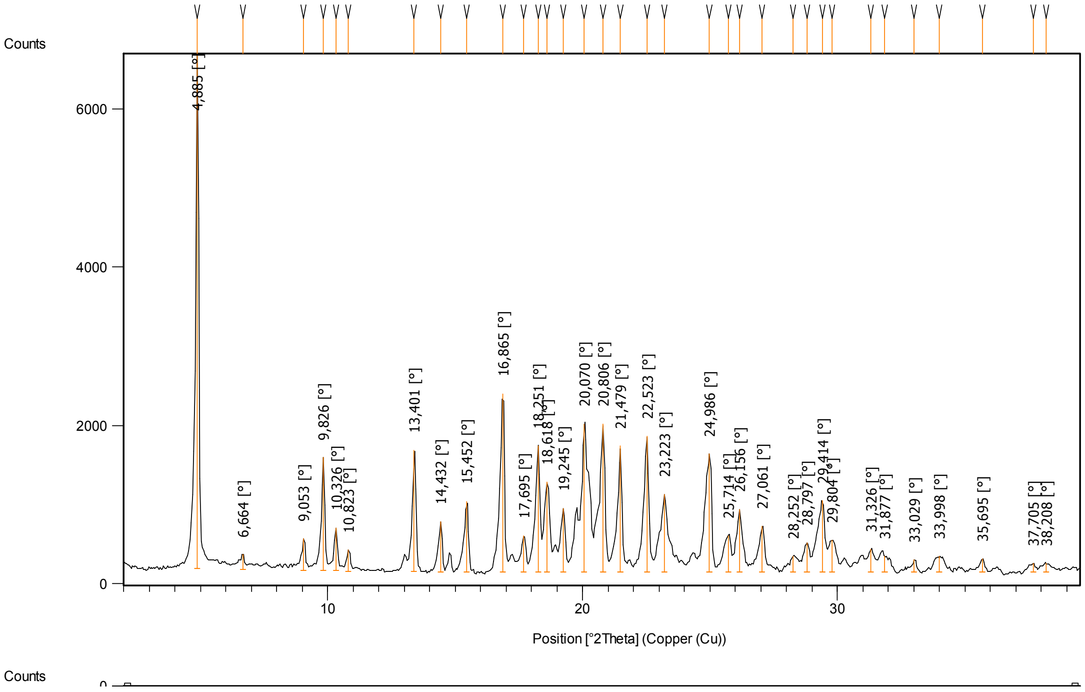


Figure 4: X-Ray powder diffraction pattern of Compound A maleate salt

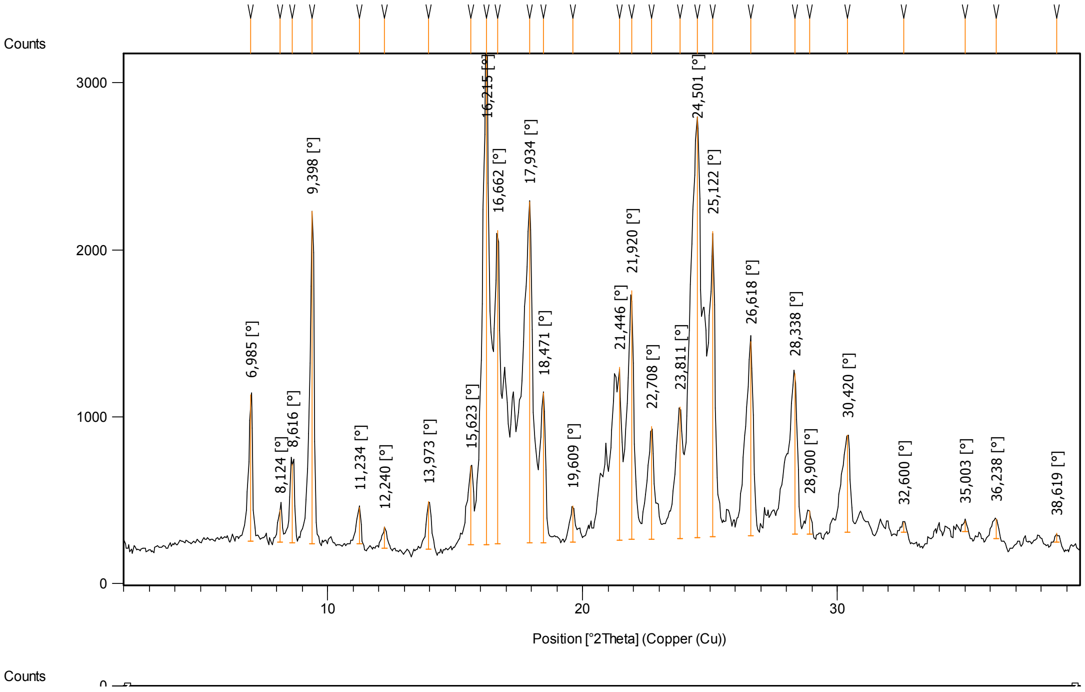


Figure 5: X-Ray powder diffraction pattern of Compound A malonate salt

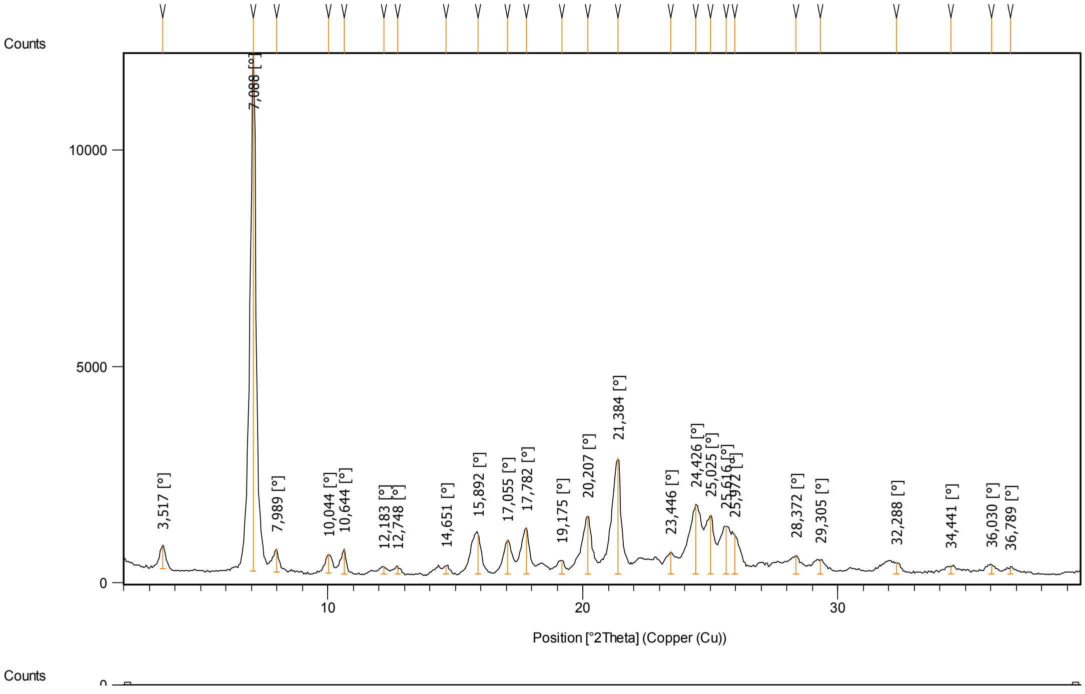


Figure 6: X-Ray powder diffraction pattern of Compound B HCl salt crystalline form II

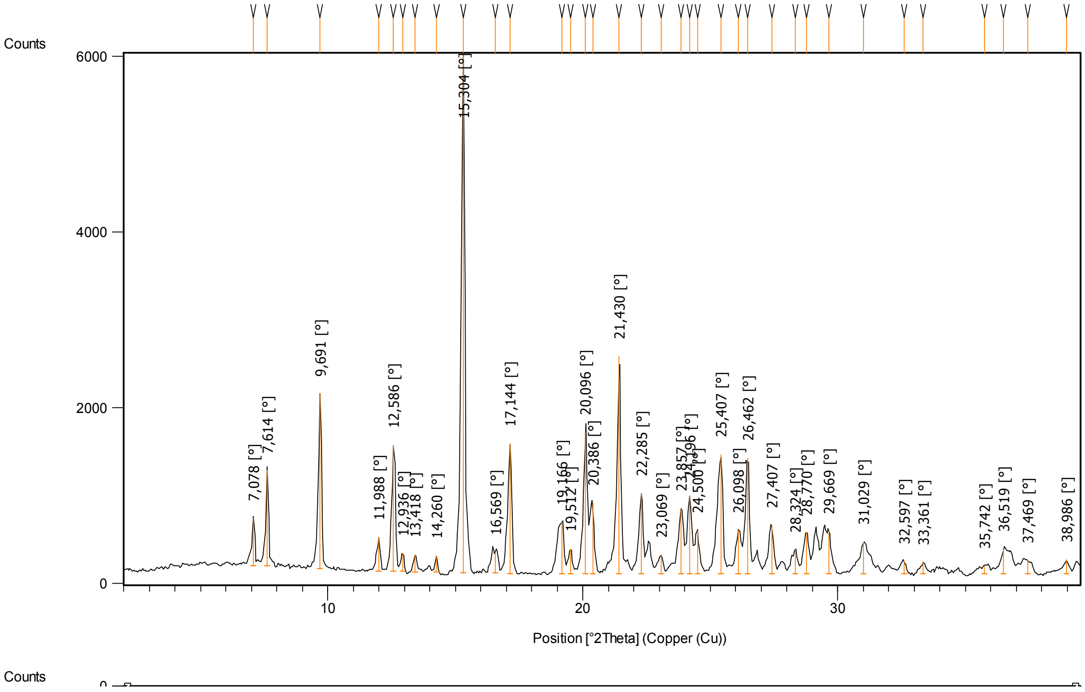


Figure 7: X-Ray powder diffraction pattern of Compound B.HCl.2H_2O crystalline form.